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Episodic Disorders: Channelopathies and Beyond

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Hereditary episodic diseases are a remarkable group of phenotypes ranging from rare muscle diseases and movement disorders to more common forms of epilepsy and migraine headache. Despite the fact that affected individuals carry the relevant mutation for their entire life, attacks occur intermittently. Patients are often completely normal between attacks.

Although on the surface these disorders appear quite different, striking similarities exist across all these diseases (**Figure 1**). In addition to these disorders being episodic, factors that can precipitate attacks overlap significantly among these disorders. Stress is the most uniform in this regard, although the specific pathway is not understood. Sleep deprivation is another—however, it is unclear whether this is simply one form of stress or whether something specific about sleep is required for maintaining homeostasis of membrane excitability in these disorders.

Certain dietary factors can lower the threshold for having an attack and include manipulations of dietary potassium, caffeine, and alcohol. Therapies that benefit patients in prevention of attacks also overlap. For example, carbonic anhydrase inhibitors decrease attack frequency for many patients with periodic paralysis, episodic ataxia, and migraine. Some anticonvulsant drugs have carbonic anhydrase inhibitory activity, although whether this activity contributes to antiseizure effects is unknown. This similarity among many different episodic diseases suggests that carbonic anhydrase inhibition may have an antiepileptic effect. Anticonvulsant drugs are also very effective in treating hyperexcitability phenotypes in many patients (e.g., seizures, paroxysmal dyskinesia, and myotonia).

The natural history of these disorders is also similar—they often come on in childhood, worsen through adolescence and young-adult life, and improve (and sometimes completely resolve) in middle- and late-adult life. The reason for this pattern is unknown. Finally, for conditions for which a clinical electrophysiological test is available, hyperexcitable phenotypes can sometimes be seen (**Figure 2**). These phenotypes include myotonia on electromyograms, cardiac arrhythmias on

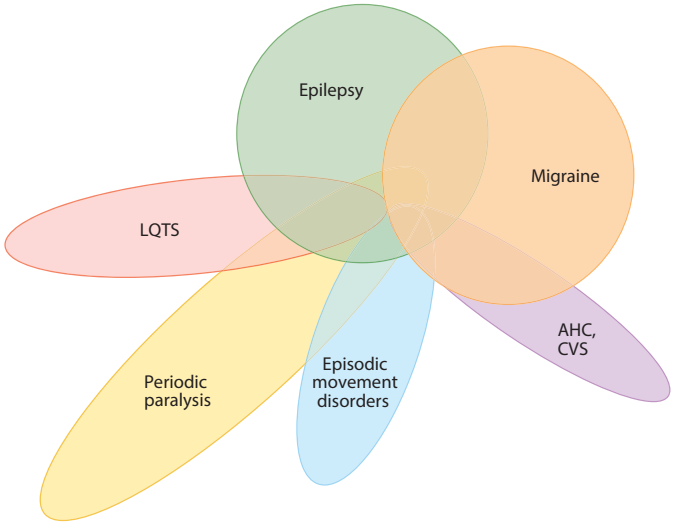

Figure 1

Many different electrical and episodic diseases affect skeletal muscle, the brain, and the heart. Although quite different in some ways, these disorders share similarities such as their episodic nature, precipitating factors, natural history, apparent hormonal influences, and therapeutic responses. Abbreviations: AHC, alternating hemiplegia of childhood; CVS, cyclic vomiting syndrome; LQTS, long-QT syndrome.

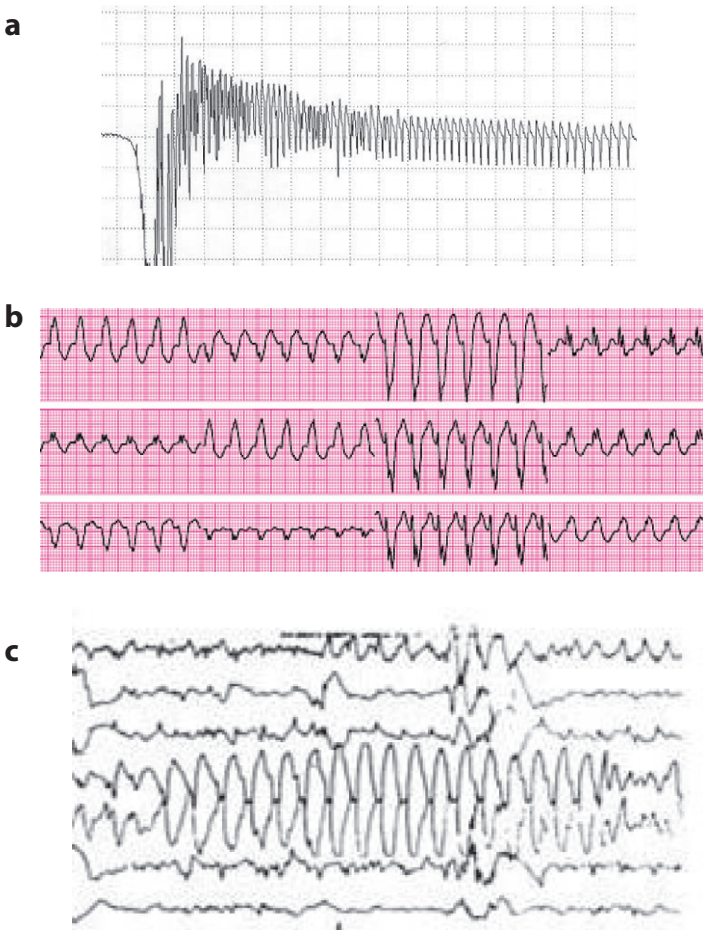

Figure 2

The physiologies of muscle, nerve, and heart tissues are somewhat different. Shown are recordings from (*a*) skeletal muscle [electromyogram (EMG)], (*b*) the heart [electrocardiogram (ECG)], and (*c*) the brain [electroencephalogram (EEG)]. Also shown are physiological abnormalities seen in some periodic paralyses (myotonia on EMG), in cardiac arrhythmias (ventricular tachycardia on ECG), and in epilepsy (focal electrographic seizure on EEG). These disorders share the abnormal physiological phenomenon of highly repetitive, organized, but abnormal activity manifest clinically as myotonia, ventricular tachycardia, or seizure. Adapted with permission from Reference 8.

electrocardiograms, and seizures on electroencephalograms. Although the physiologies of muscle, the heart, and the brain are somewhat different, all these electrophysiological findings represent abnormal, but highly organized, repetitive firing of the respective tissues.

Studies of a rare group of muscle diseases, the familial periodic paralyses, established the genetic paradigm for these episodic disorders. The first reports of channel mutations in episodic or electrical diseases were for hyperkalemic periodic paralysis and paramyotonia congenita (1–4). These developments led us to propose the term channelopathies to connote disorders of ion channels resulting from genetic mutations (5). With the cloning of the first human

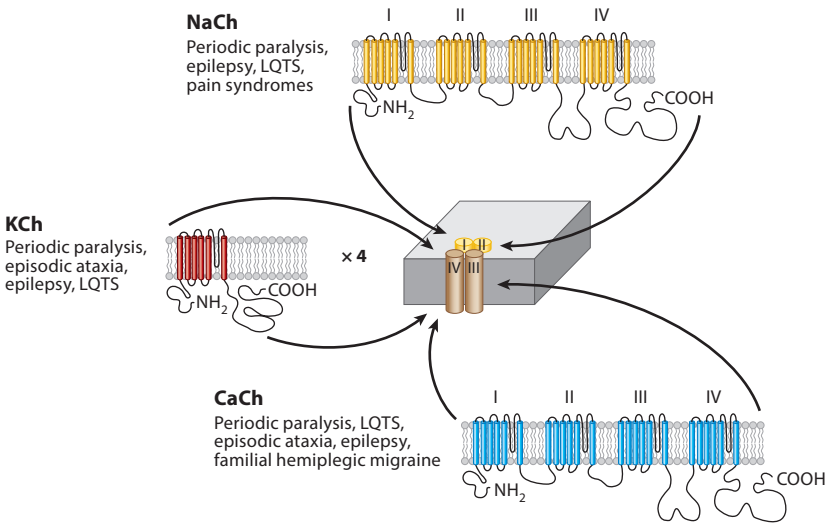

Figure 3

Voltage-gated cation channels were the first channels to be implicated in electrical disorders. Systematic study of the periodic paralyses and nondystrophic myotonias led to identification of mutations in voltage-gated sodium and calcium channels and, later, voltage-gated chloride (anion) and inwardly rectifying potassium channels. Shown here is a graphical representation of the homologous sodium (NaCh), calcium (CaCh), and potassium (KCh) channels first defined in this fascinating group of muscle diseases. KChs must tetramerize (denoted by ×4) to form functional channels. Subsequent work from many labs has shown that mutations in other genes from this family can give rise not only to muscle diseases, but also to epilepsy, migraine headache, episodic movement disorders, cardiac dysrhythmias, and peripheral sensory/pain syndromes. The symptom complex is predictably dependent on the expression pattern of the specific channel gene. Adapted with permission from Reference 8.

mutation, we had predicted that mutations in homologous genes were outstanding candidates for hereditary forms of epilepsy, cardiac arrhythmias, and peripheral nerve disorders (3). Subsequent work by our group and others has indeed shown this prediction to be true (**Figure 3**). There are now many reports of ion channel genes responsible for periodic paralyses and nondystrophic myotonias; episodic ataxias; epilepsies; hyperekplexia; familial hemiplegic migraine; and sensory syndromes like congenital insensitivity to pain, erythromelalgia, and paroxysmal itch (6, 7).

The term channelopathy has been misused by many to describe any bizarre disorder with fluctuating symptoms. We suggest that channelopathy should be reserved as a term to describe disorders in which there is molecular and genetic understanding of abnormal channel function. Clearly, all episodic disorders of the nervous system and heart ultimately result in abnormal electrical signaling. We suggest the term primary channelopathy for those cases in which mutations occur in the primary determinants of membrane excitability (e.g., voltage-gated channels, inwardly rectifying ion channels, ligand-gated channels, ion transporters, and ion exchangers) (**Figure 4**). In this special section of reviews, special attention is paid to classifying episodic or electrical disorders into primary and secondary channelopathies, acquired channelopathies, and circuit-level disorders that do not specifically affect ion channels but rather affect networks of neurons, with a net effect of abnormal electrical signaling.

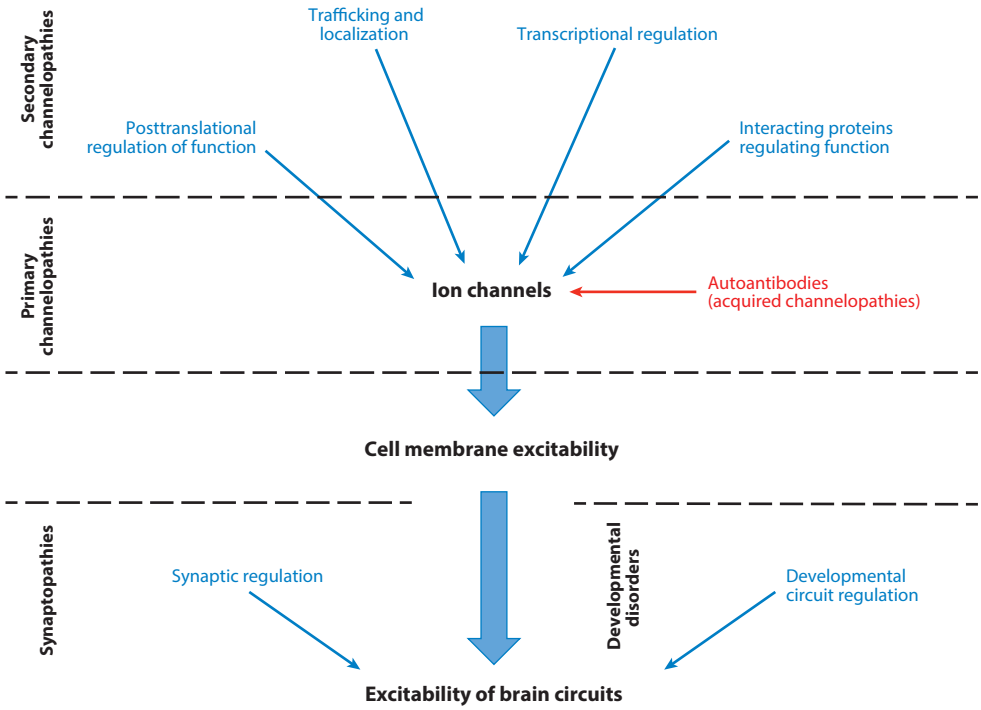

Figure 4

Proposed classification scheme for electrical and episodic disorders.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding or financial holding that might be perceived as affecting the objectivity of this review.

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